



NOTES

DNA REPLICATION & REPAIR DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Group of rare, inherited disorders; mutations in DNA maintenance, repair genes → spectrum of cancers (typically early-onset cancer diagnosis)

SIGNS & SYMPTOMS

- See individual conditions

DIAGNOSIS

LAB RESULTS

- Genetic sequencing

OTHER DIAGNOSTICS

- Family history

TREATMENT

OTHER INTERVENTIONS

- Adequate malignancy surveillance
- Minimize sun, radiation exposure

BLOOM SYNDROME

osms.it/bloom-syndrome

PATHOLOGY & CAUSES

- Rare autosomal recessive disease; extreme susceptibility to DNA damage, immune deficiency, cancer

Pathogenesis

- Instability of DNA duplexes during recombination, repair, replication → DNA mutation → oncogenesis

CAUSES

- Mutation in *BLM* gene on chromosome 15q26.1
 - Encodes RecG helicase (AKA Bloom syndrome protein): helps maintain stability of DNA when duplexes

unwound during recombination, repair, replication

RISK FACTORS

- Individuals of Ashkenazi Jewish descent

COMPLICATIONS

- Infertility (more common in individuals who are biologically male)
- Dehydration due to reflux, vomiting, diarrhea in infancy
- Immunodeficiency → secondary infection, early predisposition to cancer
- Limited intellectual ability
- Fetal intrauterine growth restriction

VISIT...

LANZAROTE
Caliente.COM

SIGNS & SYMPTOMS

- Microcephaly with proportionate small stature
- Sparse subcutaneous adipose tissue
- **Integument:** childhood rash (erythematous on nose, cheeks; worsens after sun exposure; persists 1–2 years); cafe-au-lait spots; hypopigmented skin lesions
- Facial anomalies



Figure 24.1 A male child with Bloom syndrome. He has telangiectatic facial erythema, typical of the condition.

DIAGNOSIS

LAB RESULTS

- Karyotype analysis
- Genetic testing (mutated *BLM* gene)
- ↓ immunoglobulins (IgM, IgA deficit > IgG), effector memory T-cells, memory B-cells

OTHER DIAGNOSTICS

Physical examination

- Typical facies; body habitus; integument examination (erythematous rash, hyper/hypopigmented lesions)

TREATMENT

OTHER INTERVENTIONS

- No therapeutic options

Management

- Minimize radiation exposure (MRI/ultrasound for diagnostic imaging); protect face from sun; IgG replacement for severe hypogammaglobulinemia; monitor fluid levels in infants

LI-FRAUMENI SYNDROME

osms.it/li-fraumeni_syndrome

PATHOLOGY & CAUSES

- Syndrome caused mutation of guardian of genome (*TP53*) → wide array of malignancies

Pathogenesis

- Abnormal *TP53* function → abnormal checkpoint inhibition, tumor suppression → damaged DNA cell proliferation → malignant transformation

- Abnormal *TP53* function → dysregulated apoptosis signaling → proliferation of DNA-damaged cells → malignant transformation

Diseases

- **Sarcoma**, leukemia, breast cancer, brain tumors (e.g. medulloblastomas, choroid plexus carcinomas), adrenocortical carcinoma

CAUSES

- Autosomal dominant mutation on gene TP53, located on 17p3.1 chromosome (mostly missense mutations in exons 5, 8)

COMPLICATIONS

- Radiation-associated cancers

SIGNS & SYMPTOMS

Sarcomas

- Growing, painless mass (arises with compression of surrounding structures)

Osteosarcoma

- Localized pain for several months; soft tissue mass tender to palpation, commonly of long bones (e.g. femur, humerus)

Breast cancer

- Breast mass (most common)

Brain tumors

- Focal neurologic deficit

Adrenocortical carcinomas

- Abdominal mass; hormone excess syndrome (e.g. Cushing, hyperaldosteronism, virilization, feminization)

DIAGNOSIS

LAB RESULTS

- Genetic conformational testing
- ↑ hormonal levels in functional adrenocortical carcinoma, alkaline phosphatase in osteosarcoma setting

OTHER DIAGNOSTICS

History

- Presence of malignancy
- Family history (diagnosis requires all three)
 - Sarcoma diagnosed before age 45
 - First-degree relative with any cancer before age 45
 - First/second-degree relative with any cancer before age 45/sarcoma at any age

TREATMENT

SURGERY

Resection

- Choroid plexus carcinoma (malignancy-specific therapy)

Mastectomy + radiation therapy

- Breast cancer (malignancy-specific therapy)

OTHER INTERVENTIONS

- **Management:** surveillance of individuals, family members of diagnosed individuals
 - Annual skin examination
 - Noninvasive breast cancer screening at 18–20 years
 - Regular diagnostic testing begins at 20–25
 - Colorectal cancer screening every 2–5 years, starting at 25
 - Whole body MRI recommended by American Association for Cancer Research
- Screening for
 - Individuals with breast cancer < 31 years
 - Individuals with adrenocortical carcinoma, regardless of age/family history
 - Individuals with choroid plexus carcinoma
 - Individuals with childhood sarcoma (except Ewing sarcoma)

XERODERMA PIGMENTOSUM

osms.it/xeroderma-pigmentosum

PATHOLOGY & CAUSES

- Rare autosomal recessive disease of nucleotide excision repair (NER) gene; extreme photosensitivity, early development of skin cancer
- **Pathogenesis:** UV light in setting of mutated NER gene → cross-linking of pyrimidine residues → inability for removal of covalently-linked pyrimidine residues → epithelial DNA mutation → ↑ oncogenesis risk

CAUSES

- Autosomal recessive mutation of NER gene on chromosome 9q22

COMPLICATIONS

- Basal, squamous cell carcinomas; melanoma
- **Ocular:** keratitis, opacification of cornea, iritis with synechiae formation, melanoma of choroid
- **Neurologic abnormalities:** primary neuronal degeneration
- **Radiation complications:** chromosome breakage → oncogenesis

SIGNS & SYMPTOMS

- **Extreme photosensitivity** to sunlight, abnormal pigmentation, xerosis (abnormal dryness of skin), telangiectasia, skin atrophy

DIAGNOSIS

OTHER DIAGNOSTICS

- **Clinical diagnosis:** family history, photoreactivity history, physical examination (e.g. integument, ocular examination; xerosis, skin fragility, ocular complications)

TREATMENT

OTHER INTERVENTIONS

- No curative therapy
- Avoid sun
- Sunscreen, proper clothing (minimize photoreactivity, mitigate cancer risk)
- Basal, squamous cell cancer surveillance: annual skin examination



Figure 24.2 A female child with xeroderma pigmentosum. There are numerous hyperkeratoses on the face as well as innumerable solar lentigines. Corneal scarring is also present.